Empathy or Ownership? Evidence from corticospinal modulation during pain observation

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Empathy or Ownership? Evidence from Corticospinal Modulation during Pain Observation

Giulia Bucchioni[1,2*], Carlotta Fossataro[1*], Andrea Cavallo[1], Harold Mouras[2], Marco Neppi-Modona[1], and Francesca Garbarini[1]

Abstract

■ Recent studies show that motor responses similar to those present in one's own pain (freezing effect) occur as a result of pain observation in others. This finding has been interpreted as the physiological basis of empathy. Alternatively, it can represent the physiological counterpart of an embodiment phenomenon related to the sense of body ownership. We compared the empathy and the ownership hypotheses by manipulating the perspective of the observed hand model receiving pain so that it could be a first-person perspective, the one in which embodiment occurs, or a third-person perspective, the one in which we usually perceive the others. Motor-evoked potentials (MEPs) by TMS on M1 were recorded from first dorsal interosseous muscle, whereas participants observed video clips showing (a) a needle penetrating or (b) a Q-tip touching a hand model, presented either in first-person or in third-person perspective. We found that a pain-specific inhibition of MEP amplitude (a significantly greater MEP reduction in the "pain" compared with the "touch" conditions) only pertains to the first-person perspective, and it is related to the strength of the self-reported embodiment. We interpreted this corticospinal modulation according to an "affective" conception of body ownership, suggesting that the body I feel as my own is the body I care more about. ■

INTRODUCTION

In the first decade of the 21st century, the mirror neurons paradigm (Rizzolatti, Cattaneo, Fabbri-Destro, & Rozzi, 2014) has exercised a strong influence in cognitive neuroscience, and from the domain of action where it was discovered, a "mirror-matching" simulation mechanism has been extended to other domains, including emotional experience (Keysers et al., 2004; Singer et al., 2004; Gallese, 2003). According to this mechanism, the emotional state of an individual activates corresponding representations in another individual observing that state. In a seminal paper, Avenanti, Bueti, Galati, and Aglioti (2005) demonstrated that motor responses, similar to those present in one's own pain (i.e., freezing effect), occur as a result of pain observation in others. Consistent with the "mirror-matching" simulation theory, this finding has been interpreted as the neurophysiological basis of empathy for other's pain (Singer & Frith, 2005). According to this view, the brain could use self-representation as a reference for perception of painful events occurring to others' body by "mapping external stimuli onto one's own body" (Avenanti et al., 2005).

In the Avenanti and colleagues (2005) paper, as well as in a series of further papers (Avenanti, Sirigu, & Aglioti, 2010; Avenanti, Minio-Paluello, Bufalari, & Aglioti, 2009; Avenanti, Minio-Paluello, Minio Paluello, Bufalari, & Aglioti, 2006; Avenanti et al., 2005), motor-evoked potentials (MEPs) were recorded from the first dorsal interosseous (FDI) muscle, whereas participants observed video clips showing either a needle penetrating or a Q-tip touching a hand model. The main finding of these studies was a pain-specific freezing effect, that is, a significant decrease of the MEP amplitude in the needle compared with the Q-tip condition. It is important to note that the specificity of this freezing effect has been extensively described (Avenanti et al., 2005, 2006). To investigate the muscle selectivity, MEPs were recorded either from the hand muscle underlying the skin region penetrated/touched by the needle/Q-tip (FDI) or from a nearby hand muscle (abductor digiti minimi, ADM). The pain-specific freezing effect was present in FDI and not in ADM, suggesting a high specificity of the effect related to the recording muscle. To investigate the body part selectivity, MEPs were recorded from the hand muscles while different stimuli were presented: needle/Q-tip penetrating/touching different body parts, such as hand or foot, or a noncorporeal object, such as a tomato. The effect was present for the observation of a needle entering the hand and absent during the observation of a needle entering the feet or a noncorporeal object, suggesting a high specificity of the freezing effect related to the observed body part. A number of other variables have also been manipulated, such as the stimulus intensity (e.g., hand penetrated by a needle vs.

[1]University of Turin, [2]Université de Picardie Jules Verne, Amiens Cedex 1, France

*These authors contributed equally to this work, and both should be considered first authors.

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hand pin-picked; Avenanti et al., 2006), the observed hand congruency (e.g., right vs. left; Avenanti, Minio-Paluello, Sforza, & Aglioti, 2009), and the observed hand race (e.g., in-group vs. out-group; Avenanti et al., 2010). However, to the best of our knowledge, the stimulus presentation perspective has never been investigated, and the hand model has always been presented in a first-person perspective.

In recent years, the increasing interest for the concept of body ownership (i.e., the belief that a specific body part belongs to one's own body; e.g., Tsakiris, 2010) pays specific attention to the relation between the perspective through which a body part is observed and the possibility for the participants to experience it as part of their own body (i.e., embodiment phenomenon). Converging evidence, coming from experimental manipulations in healthy participants (e.g., rubber hand illusion [RHI]; Kalckert & Ehrsson, 2012; Petkova, Khoshnevis, & Ehrsson, 2011; Makin, Holmes, & Ehrsson, 2008; Costantini & Haggard, 2007; Tsakiris & Haggard, 2005; Ehrsson, Spence, & Passingham, 2004) and in pathological conditions after brain damage (e.g., delusion of body ownership; Garbarini et al., 2013, 2014, 2015), shows that embodiment occurs only when the rubber/alien limb is located in a position coherent with the participants' higher-order and preexisting body representation, whenever it is perceived from a first-person perspective.

In this study, we aimed at disentangling the empathy and the ownership hypothesis by manipulating the perspective of the observed hand model receiving pain, so that it could be a first-person perspective, the one in which embodiment occurs, or a third-person perspective, the one in which, in everyday life, we perceive the body parts of others (Ruby & Decety, 2001). If the pain-specific corticospinal modulation, found by the Avenanti and colleagues studies when stimuli were presented in a first-person perspective, also occurs in a third-person perspective, this would confirm the empathy for others' pain hypothesis. Alternatively, a perspective-dependent effect, only related to the first-person viewpoint, would suggest that this pain-specific corticospinal modulation represents the physiological counterpart of an embodiment phenomenon, related to the sense of body ownership. Likewise, a correlation between physiological measures and empathic traits may confirm the empathy hypothesis; conversely, a correlation with a measure of subjective embodiment disposition, as that obtained by means of the RHI paradigm, may support the bodily ownership hypothesis.

METHODS

Participants

Twenty participants took part in the experiment (12 women; mean age ± *SD* = 24.3 ± 3.34 years, range = 20–36 years). Because of technical problems during MEP recording and participants' availability to complete the experiment, four participants were excluded from the analysis, resulting in a sample of 16 participants (10 women; mean age ± *SD* = 24.12 ± 3.7 years, range = 20–36 years). All were right-handed according to the Standard Handedness Inventory (Oldfield, 1971), with normal or corrected-to-normal visual acuity. None of them had a history of neurological, major medical, or psychiatric disorders, and they were free from any contraindication to TMS (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). Before starting the experimental session, each participant was naive as to the purposes of the study and signed an informed consent; information about the study purpose was provided only at the end of the experimental session. The experimental procedure was granted ethical approval by the Ethics Committee of the University of Turin and was carried out in accordance with the principles of the revised Helsinki Declaration (World Medical Association General Assembly, 2008). None of the participants reported discomfort or adverse effects during TMS acquisitions.

Stimuli

Four different color video clips were used as experimental stimuli: (i) a right hand presented in first-person perspective deeply penetrated by a needle on the FDI muscle ("pain first-person"), (ii) a right hand presented in third-person perspective deeply penetrated by a needle on the FDI muscle ("pain third-person"), (iii) a right hand presented in first-person perspective touched by a Q-tip on the FDI muscle ("touch first-person"), and (iv) a right hand presented in third-person perspective touched by a Q-tip on the FDI muscle ("touch third-person"). Moreover, two further video clips were used as baseline condition: (a) a dorsal view of a right hand presented in first-person perspective ("baseline first-person") and (b) a dorsal view of a right hand presented in third-person perspective ("baseline third-person").

TMS Stimulation and EMG Recording

TMS is a noninvasive brain stimulation technique extensively used in cognitive neuroscience (Miniussi, Harris, & Ruzzoli, 2013). In this study, TMS pulses were administered using a Magstim Rapid2 stimulator (Magstim, Whitlan, Dyfed, Wales, UK) connected to a 70-mm figure-of-eight coil positioned over the left primary motor cortex (M1) hand region. The coil was held tangentially to the scalp with the handle pointing backwards and laterally 45° away from the mid-sagittal line, such that the flow induced by the second most effective phase of the biphasic pulse moved in a posterior anterior direction (Di Lazzaro et al., 2001; Kammer, Beck, Thielscher, Laubis-Herrmann, & Topka, 2001). This orientation permits the lowest motor threshold, optimizing the stimulation (Brasil-Neto, Pascual-Leone, Valls-Sole, Cohen, & Hallett, 1992). Before the recording session, the coil was moved in steps of 1 cm over the left motor cortex to determine the individual optimal position (OSP) from which maximal MEP amplitudes were elicited in FDI. Once the OSP was found, the individual resting motor threshold (rMT) was determined as the lowest stimulus intensity that induced at least five MEPs (at list 50 μV peak-to-peak amplitude) of 10 consecutive TMS pulses in the recorded muscle (Rossini et al., 2015). Mean rMT was 58% (ranging from 41% to 78%) of maximum stimulator intensity. During the recording session stimulation, intensity was set at 115% of the rMT. MEPs were recorded from the FDI muscle of the participant's right hand. The registration of this muscle was selected because it is the same muscle penetrated by a needle or touched by a Q-tip in the presented video clips. EMG activity was recorded by pairs of Ag–AgCl surface electrodes (11 mm diameter; EL503) connected to a Biopac MP-150 electromyograph (Biopac Systems, Inc., Santa Barbara, CA). They were placed in a classical belly–tendon montage: the active electrode over the muscle belly and the reference electrode over the associated joint or tendon. The ground was placed over the participant's left elbow. The EMG signals were acquired at 10 kHz sampling rate, amplified, filtered with a band-pass (10–500 Hz) and a notch (50 Hz) filter, and stored on a PC for offline analysis.

Experimental Procedure

TMS Experiment

The experiment was carried out in a dimly illuminated room where participants were seated in a comfortable armchair with their head positioned on a fixed head rest. A single experimental session lasted 1 hr 45 min approximately, and each session was divided in two blocks. The task (see Figure 1) consisted in watching video clips displayed on a 17-in. monitor (resolution = 1280 × 780 pixels, refresh frequency = 60 Hz, background luminance = 0.5 cd/m^2) placed at a distance of 80 cm. Participants were instructed to lay motionless on the armchair and to keep their hands in a prone position on a pillow,

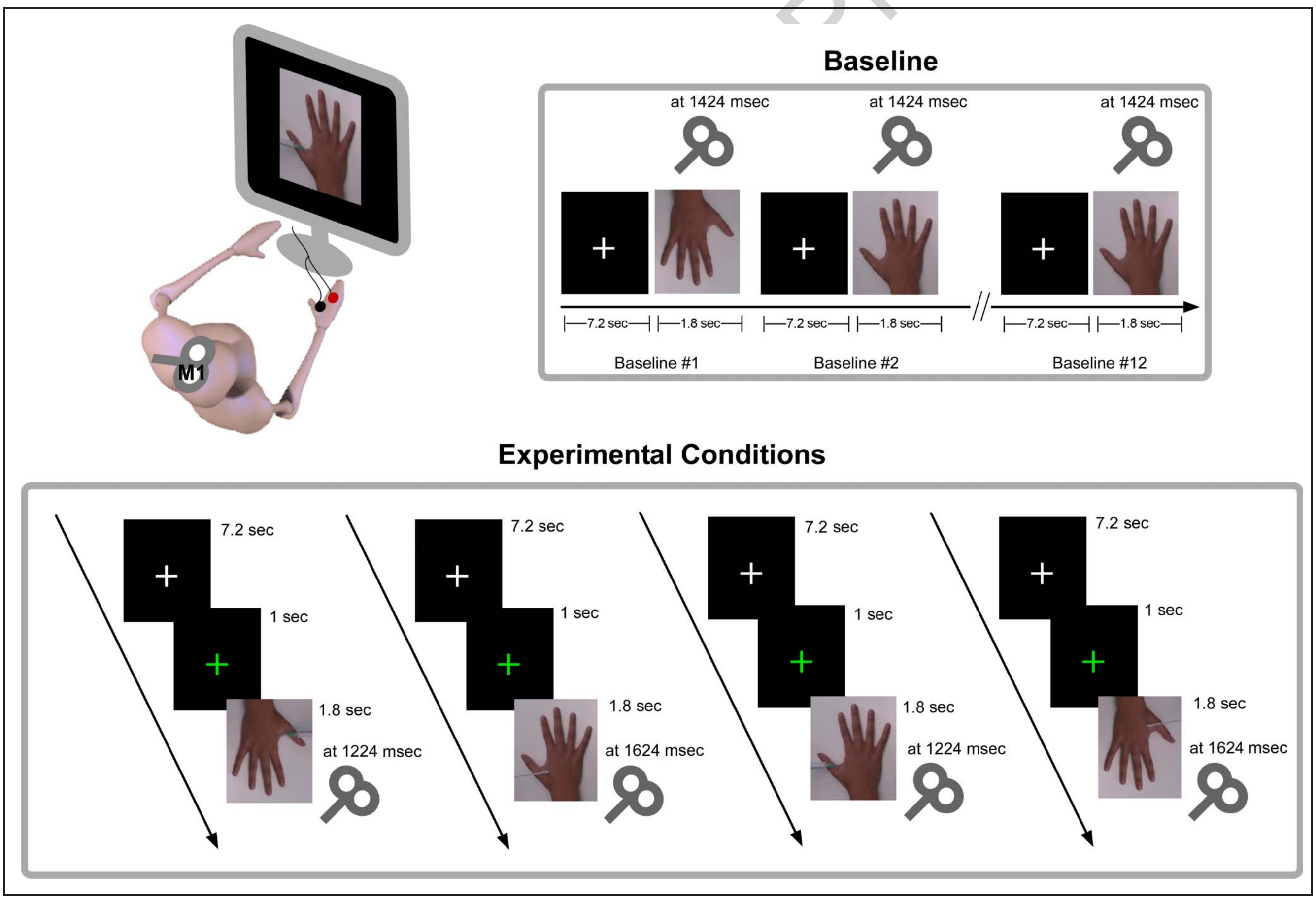


Figure 1. Schematic representation of the experimental protocol and design. Top left: A graphic representation of the experimental setting. A participant watching the video stimuli, presenting hand models in a first- or third-person perspective, while TMS pulses were delivered over the left M1. Top right: The stimuli presented in the baseline conditions. A static hand was randomly presented either in the first- or third-person perspective. TMS pulses were delivered 1424 msec after stimulus onset. Bottom: The stimuli presented in the experimental conditions. The hand model, presented in a first- or third-person perspective, penetrated by a needle or touched by a Q-tip. TMS pulses were delivered at two possible time points: early time (200 msec after needle penetration/Q-tip touch; i.e., at 1224 msec after stimulus onset) and late time (600 msec after needle penetration/Q-tip touch; i.e., at 1624 msec after stimulus onset).

trying to relax the muscles as much as possible. TMS-induced MEPs from the right FDI muscle were acquired once for each video presentation at one of two possible time points: early time (200 msec after needle penetration/Q-tip touch) and late time (600 msec after needle penetration/Q-tip touch). These stimulation times correspond to the earliest and the latest stimulation times used in previous experiments (Avenanti et al., 2005, 2006, 2010; Avenanti, Minio-Paluello, Bufalari, et al., 2009; Avenanti, Minio-Paluello, Sforza, et al., 2009), where the TMS pulse was randomly triggered between 200 and 600 msec before the end of the video clip. Here, capitalizing on the results of previous studies (Borgomaneri, Gazzola, & Avenanti, 2014; Fecteau, Pascual-Leone, & Théoret, 2008), we controlled the time variable, stimulating at two defined time points (early; late), because the literature recently evidenced two different phases in the functional modulation of the motor cortex: An earlier time of stimulation should evidence an orienting response; a later time of stimulation might represent motor resonance. Each video clip presentation was followed by 8200 msec of intertrial interval: A white fixation cross was presented for 7200 msec and was then replaced by a green cross (1000 msec), prompting the participant to watch the new video clip. Each video clip lasted 1800 msec. For each block, video clips of each condition were presented nine times in a random order, resulting in a total of 72 trials (4 video clips $\times$ 9 repetitions $\times$ 2 time points). Baseline measures of the corticospinal excitability were also assessed prior to and following the video presentations by means of two supplementary series of 12 MEPs. A static hand was randomly presented six times for each of the two perspectives (first-person and third-person). TMS stimulation was delivered 1424 msec after stimulus onset. Thanks to these series of MEP registrations, we checked for any corticospinal excitability change related to TMS per se between the beginning and the end of each experimental block; these MEP average amplitudes were calculated to set individual baselines for data normalization. The stimulus presentation timing, EMG recording, and TMS triggering, as well as stimuli randomization, were controlled by E-Prime V2.0 software (Psychology Software Tools, Inc., Pittsburgh, PA) running on a PC.

Self-report Measures of Empathy, "Self-recognition," and "Body Ownership"

To investigate the subjective trait of empathy, we administered the Italian version (Bonino, Coco, & Tani, 2010) of the Interpersonal Reactivity Index (IRI; Davis, 1983), which is a self-report multidimensional psychometric measure composed of 28 items designed to measure both cognitive and emotional components of empathy. Participants rated each item on a 5-point Likert scale, ranging from "Does not describe me well" to "Describes me very well". The scale has four subscales (each made up of seven different items): Perspective Taking (e.g., "When I am upset at someone, I usually try to 'put myself in his shoes' for a while"), Fantasy Scale (e.g., "I really get involved with the feelings of the characters in a novel"), Empathic Concern (e.g., "When I see someone being taken advantage of, I feel kind of protective towards them"), and Personal Distress (e.g., "In emergency situations, I feel apprehensive and ill-at-ease"). Each subscale score ranges from 0 to 28.

To investigate the contribution of a self-recognition mechanism, suggestive of the tendency of participants to recognize the hand on the screen as a video representation of their own hand and of the presence of a proper illusory experience of bodily ownership, an ad hoc two-question questionnaire was administered. Four videos, each one representative of a single experimental condition (pain first-person, pain third-person, touch first-person, touch third-person), were shown to participants along with two items referred to the specific condition shown. Item 1 (i.e., self-recognition question): "I felt as if the touch/prick was delivered to the hand I recognized as mine." Item 2 (i.e., body ownership question): "I felt as if the hand penetrated/touched in the video was part of my own body." Participants were asked to rate their agreement/disagreement with these questions by using a 7-point Likert scale, ranging from -3 (i.e., *I don't agree at all*) to 3 (i.e., *I totally agree*), with "0" corresponding to neither agreeing nor disagreeing.

RHI Experiment

To measure the subjective embodiment disposition in our sample, an additional experiment employing the RHI (Botvinick & Cohen, 1998) procedure, known to modulate the sense of bodily ownership in healthy participants, was carried out. The role of the perspective through which the rubber hand is perceived in modulating the strength of the embodiment has also been investigated (Kalckert & Ehrsson, 2012; Petkova et al., 2011; Ehrsson et al., 2004). We employed a black wooden box (60 $\times$ 40 $\times$ 20 cm) divided in halves (30 $\times$ 30 $\times$ 20 cm) by a perpendicular panel. One of the halves was open to the view to allow sight of the rubber hand, whereas the other half prevented the sight of the participant's real hand. Two square holes (12 $\times$ 12 cm) placed on both horizontal sides of the box accommodated the participant's arm and the rubber hand. A black towel covered the participant's shoulders and the proximal end of both the real and the rubber hand to create the illusion that the rubber hand was jointed to the participant's body. A wooden panel (30 $\times$ 30 cm) was used to cover the top of the box at the end of each experimental condition. The box was placed in front of the participant's chest (at a distance of about 15 cm) and disposed to have the rubber hand aligned with the participants' right shoulder. Before starting, participants were familiarized with the setting and instructed about all the procedures and the rating scales. The participants' right arm was placed inside the portion of the box hidden to the view; the palm was facing down, and the fingers were stretched out. In the other portion of the box, open to the view, was placed a right rubber hand (at a distance of approximately 25 cm from the participant's hand), exactly where the participants' hand had to be. During each experimental condition, participants were asked to look attentively at the rubber hand index finger waiting for the forthcoming stimulations of the rubber hand's index finger (with a brush) for 180 sec. All participants underwent all conditions, which comprised different experimental setups according to the perspective from which the rubber hand was observed (first- or third-person perspective) and the type of stimulation (synchronous or asynchronous condition). In summary, there were four conditions (first-person synchronous, third-person synchronous, first-person asynchronous, third-person synchronous), and the condition sequence was counterbalanced among participants (see Figure 5, left). After each condition, participants were asked to answer to a questionnaire about the illusion experience. The questionnaire was composed of eight items (Kalckert & Ehrsson, 2012; see Table 1). Four (I1–I4) served to capture different aspects of the illusory perception (e.g., the sensation of touches on the rubber hand and the change in the beliefs of ownership of that hand), and four (I5–I8) served as control items to assess task compliance and susceptibility effects. Participants had to rate their agreement/disagreement on a 7-point Likert scale with ranging from "+3" (*agree very strongly*) to "−3" (*disagree very strongly*), where "0" corresponded to neither agreeing nor disagreeing. To avoid any possible carryover effects of the illusion, after each condition participants rested for about 60 sec.

Data Analysis

To prevent contaminations of MEPs by background EMG activity, trials with any background activity greater than

Table 1. The Questionnaire, Consisting of Eight Statements Divided in Real and Control Items (Kalckert & Ehrsson, 2012)

1. I felt as if I was looking at my own hand.
2. I felt as if the rubber hand was part of my body.
3. It seemed as if I were sensing the touch of the paintbrush in the location where I saw the rubber hand touched.
4. I felt as if the rubber hand was my hand.
5. I felt as if my hand was turning rubbery.
6. It seemed as if I had more than one right hand.
7. I appeared as if the rubber hand were drifting toward my real hand.
8. I felt as if I had no longer a right hand, as if my right hand had disappeared.

50 μV in the 100-msec window preceding the TMS pulse were excluded from the MEP analysis. EMG data were collected for 300 msec after the TMS pulse. Data were analyzed offline using AcqKnowlege software (Biopac Systems, Inc., Santa Barbara, CA) and Statistica Software 6.0 (StatSoft, Inc., Tulsa, OK). Averaged peak-to-peak amplitudes of MEPs recorded on FDI were computed separately for each condition (pain first-person, pain third-person, touch first-person, touch third-person) and for the two stimulation conditions (early and late). MEP amplitudes deviating more than 2 standard deviations from the mean for each condition and trials contaminated by muscular preactivation were excluded from the analyses and considered as outliers (2%).

To control for the possible effect of TMS per se in modulating corticospinal excitability, a preliminary analysis was conducted by means of a 2 × 2 × 2 repeated-measure ANOVA on the baseline mean raw MEP values with perspective (first-person, third-person), block (first, second), and session (before, after the experimental block) as within-subject factors. In the main analysis of the physiological data, for each block, the MEP values recorded from each experimental condition were averaged and normalized as percentage of the mean MEP value recorded from the baseline condition of each experimental block (MEP ratio = $MEP_{obtained}/MEP_{baseline} \times 100$). Normalized data were entered into a 2 × 2 × 2 repeated-measure ANOVA with perspective (first-person, third-person), time of stimulation (early, late), and valence of stimuli (pain, touch) as within-subject factors. Post hoc comparisons were performed by means of Duncan test.

For both the "self-recognition" and the "body ownership" item, the participants' rating scores in each condition were averaged and entered into a 2 × 2 repeated-measures ANOVA, with valence of stimuli (pain, touch) and perspective (first-person, third-person) as within-subject experimental factors. To investigate single contrasts of interest, planned comparisons were performed. To examine whether a relation existed between the physiological data (MEP values in the pain first-person condition at the late time of stimulation) and behavioral data (self-recognition and body ownership ratings in the pain first-person condition), we also performed a linear regression where the normalized MEP values were used to predict the questionnaire ratings. Finally, according to the Avenanti and colleagues (2005) method, for correlation analyses with the scores obtained at the IRI subscales, we computed an index of MEP amplitude change as follows: MEP amplitude during the pain condition minus amplitude during the corresponding (first-person or third-person) baseline condition divided by the average of the same two conditions. For each pain condition (early pain first-person, early pain third-person, late pain first-person, late pain third-person), the obtained values were used to predict the scores obtained at the IRI subscales.

For the RHI questionnaire, in each condition the participants' rating scores (normalized in z scores) were averaged and entered into a 3 × 2 repeated-measure ANOVA, with stimulation (synchronous, asynchronous), perspective (first-person, third-person), and items (real, control) as within-subject experimental factors. Post hoc comparisons were carried out using the Duncan test. Furthermore, we performed a linear regression, where the normalized MEP values (of the first-person condition in the late time of stimulation) were used to predict the strength of the illusion, which was expressed as an index calculated by using only the real item ratings in the first-person condition and expressed as the difference between ratings during the synchronous and the asynchronous condition.

RESULTS

EMG Results

Preliminary analysis on the MEPs acquired during the baseline conditions showed neither significant main effects nor interactions. This means that (a) nonspecific perspective effects were absent (Perspective: $F(1, 15) = 0.22$, $p = .64$), (b) the cortical excitability was unchanged in the second compared with the first experimental block (Block: $F(1, 15) = 0.9$, $p = .76$), and (c) TMS per se did not induce any change in corticospinal excitability (Session: $F(1, 15) = 1.47$, $p = .24$).

Repeated-measures ANOVA on normalized MEP amplitudes revealed a significant interaction among perspective, time of stimulation, and valence of stimuli ($F(1, 15) = 5.08$, $p = .039$; see Figure 2). This indicates that a pain-specific inhibition of MEP amplitude (i.e., a significantly greater MEP reduction in the pain compared with the touch condition) only pertains to the late time of stimulation and to the first-person perspective (MEP mean amplitude ± *SD*: late touch first-person = 0.95 ± 0.49; late pain first-person = 0.65 ± 0.21; $p = .007$). No difference between pain and touch conditions was found at the early time of stimulation or when stimuli were presented in third-person perspective. Overall, the MEP amplitude in the late pain first-person conditions was significantly lower with respect to all the other conditions ($p < .05$ for each post hoc comparison). It is interesting to note that a significant difference between first- and third-person perspective only pertains to the pain condition in the late time of stimulation (MEP mean amplitude ± *SD*: late pain first-person = 0.65 ± 0.21; late pain third-person = 0.86 ± 0.38; $p = .038$). No significant perspective effect was found in the early time of stimulation or for the touch conditions. Examples of MEPs recorded from the FDI muscle of a representative participant are shown in Figure 2.

Self-report Measures Results and Correlations with Physiological Data

The repeated-measure ANOVA on the scores of the "self-recognition" item showed a main effect of the valence of stimuli ($F(1, 15) = 23.57$, $p = .0002$) and perspective ($F(1, 15) = 22.1$, $p = .0003$), indicating a higher rating in pain compared with touch stimuli (mean ± *SD*: pain = 0.15 ± 1.85; touch = −1.21 ± 1.73) and in first-person compared with third-person perspective (mean ± *SD*: first-person = −0.08 ± 1.73; third-person = −1.25 ± 1.83). The repeated-measure ANOVA on the scores of the "body ownership" item showed a main effect of the valence of stimuli ($F(1, 15) = 5.51$, $p = .03$) and perspective ($F(1, 15) = 16.97$, $p = .0009$), indicating a higher rating in pain compared

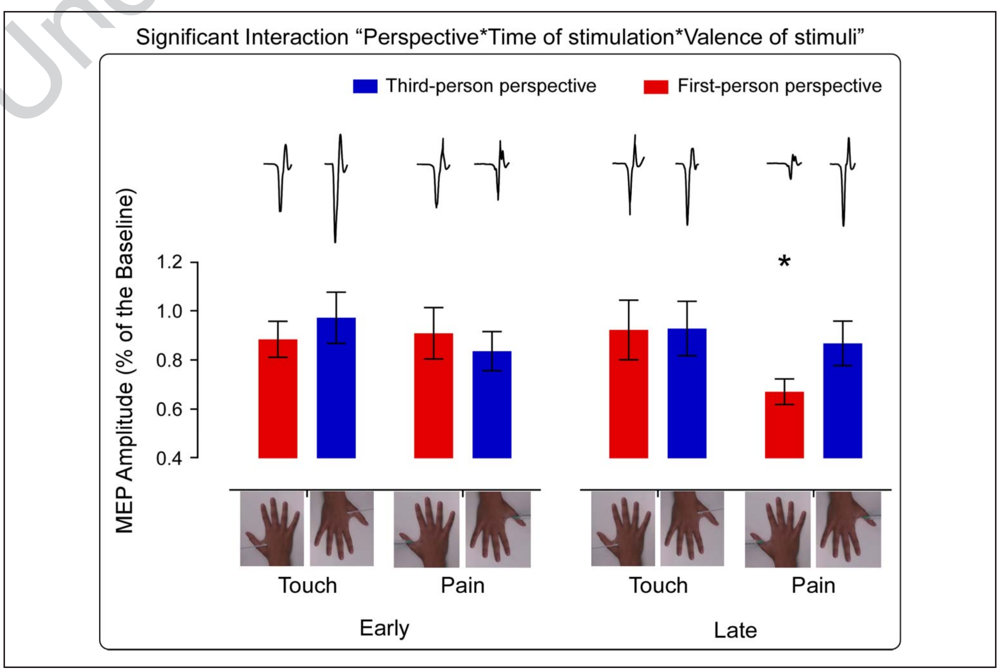
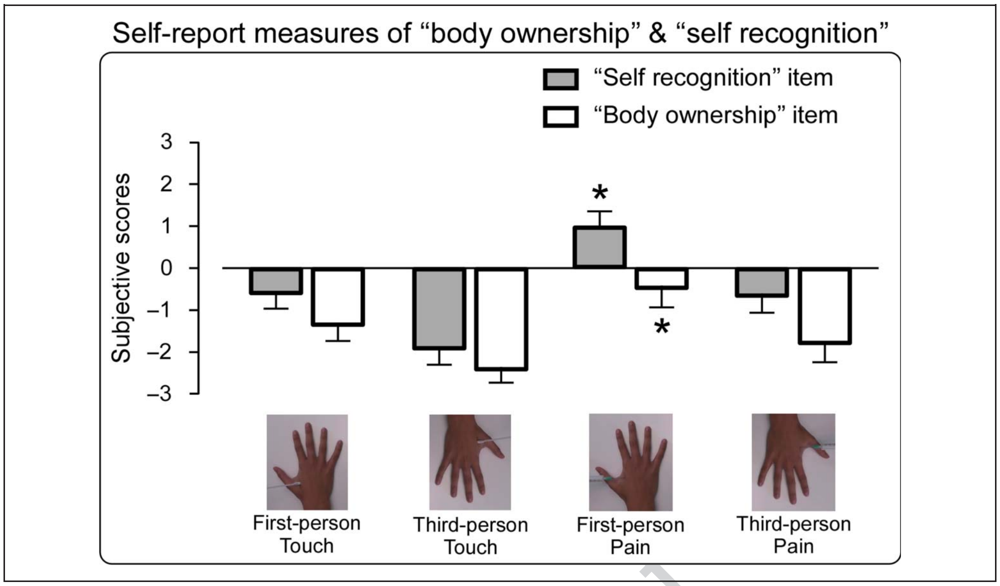


Figure 2. MEP results. The graph shows the mean MEP amplitudes, expressed as percentage of the baseline, in the four experimental conditions (Pain first-person, Pain third-person, Touch first-person, Touch third-person) and in the two times of stimulation (Early, Late). Error bars indicate *SEM* ($*p < .05$). Raw MEP amplitudes recorded from FDI muscle in one representative participant during different experimental conditions at the late time of stimulation.

Figure 3. Self-report measure of "self-recognition" and "body ownership." The graph shows the mean subjective scores in the four experimental conditions (Pain first-person, Pain third-person, Touch first-person, Touch third-person). Error bars indicate *SEM* (*$p < .05$).



with touch stimuli (mean ± *SD*: pain = −0.09 ± 2.08; touch = −1.84 ± 1.7) and in first-person compared with third-person perspective (mean ± *SD*: first-person = −1.16 ± 1.94; third-person = −2.06 ± 1.74). Finally, both in the "self-recognition" and "body ownership" items, the mean score in the pain first-person condition was the highest and was significantly different compared with all other conditions ($p < .05$ for each planned comparison; see Figure 3).

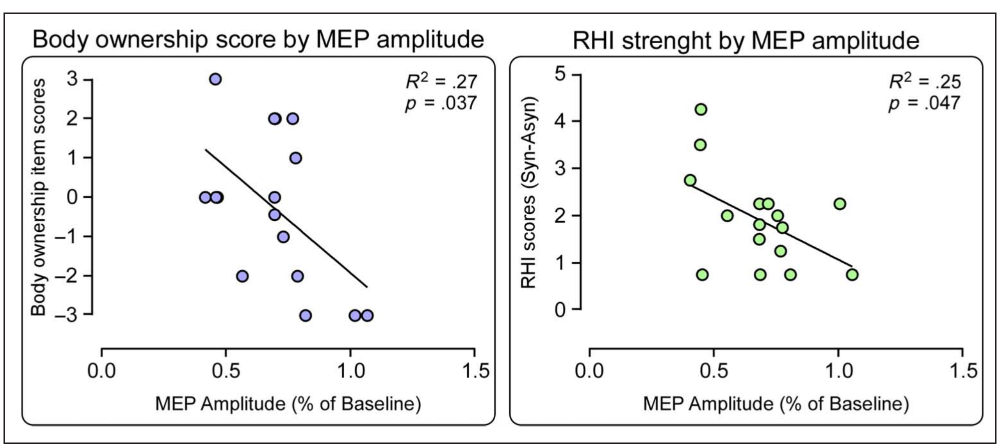
According to the linear regression analysis, the normalized MEP values, recorded at the late time of stimulation in the pain first-person condition, were significantly related to the ratings reported in the body ownership item: The smaller the MEP amplitude, the higher the "body ownership" score over the observed hand model ($R^2 = 0.27$; $p = .037$); see Figure 4, left). Conversely, no significant relation with the ratings reported in the self-recognition item was found. For what concern the IRI questionnaire scores, no significant correlation was found with the index of MEP amplitude change.

RHI Results and Correlations with Physiological Data

The repeated-measure ANOVA on the RHI subjective rating revealed a significant interaction among stimulation, perspective, and items ($F(1, 15) = 20.05, p = .0004$). This result indicates that a specific RHI effect only pertains to the real items (I1–I4) after synchronous stimulation in the first-person perspective (i.e., the strength of the illusion is significantly greater in real items after synchronous stimulation in first-person compared with all other conditions; $p < .0002$ for each comparison; see Figure 5).

The linear regression analysis revealed that normalized MEP values in the pain first-person condition significantly predicted the extent to which participants experienced the illusion of ownership over the rubber hand in the

Figure 4. Left: Linear regression "body ownership score by MEP" amplitude. The MEP amplitude, at the late time of stimulation, was used as independent variable to predict the feeling of body ownership over the hand model reported on a 7-point Likert scale. Right: Linear regression "RHI strength by MEP" amplitude. The MEP amplitude, at the late time of stimulation, was used as independent variable to predict the strength of the RHI expressed as difference between asynchronous and synchronous condition.



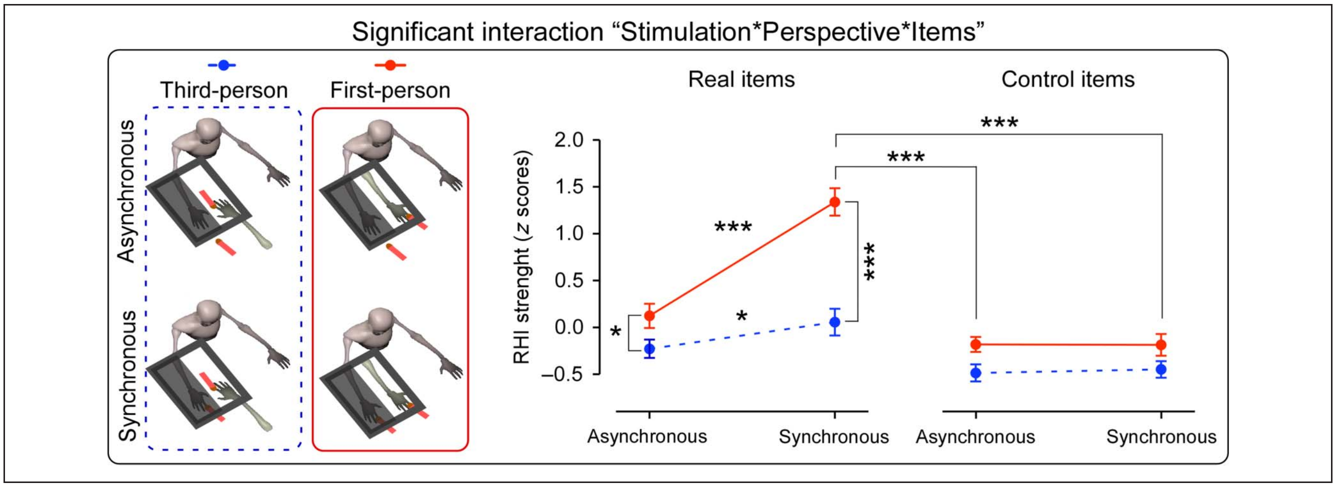


Figure 5. Left: Schematic representation of the RHI experimental design and setting. A participant watched a right rubber hand either in first- or third-person perspective being touched synchronously or asynchronously with the real hand. Right: RHI ANOVA results. Significant interaction among stimulation, perspective, and items. Subjective rating scores are expressed as z scores. Error bars indicate *SEM* (*p < .05, ***p < .0005).

synchronous first-person condition ($R^2 = 0.25$; $p = .047$). This suggests that the stronger the inhibition effect observed in MEP amplitude is, the greater is the subjective embodiment disposition during the RHI (see Figure 4, right).

DISCUSSION

In this study, we asked whether pain-specific motor responses occurring during pain observation can represent, as previously suggested (Avenanti et al., 2005), the physiological basis of empathy or, alternatively, can be better explained by an embodiment mechanism related to the sense of body ownership. To answer this question, we manipulated the perspective of the observed hand model receiving pain, whereas MEPs to single-pulse TMS on left M1 were recorded from the right FDI muscle. According to the Avenanti and colleagues studies, a pain-specific corticospinal modulation can be described as a significant decrease of the MEP amplitude in pain compared with touch conditions. However, our results show that this motor response only pertains to the late time of stimulation and, most importantly, to the first-person perspective.

The evidences concerning the onset of the modulation of the corticospinal excitability after an observed action are rather contradictory. Although some studies show that modulation of TMS-induced MEPs can occur 60–90 msec after the salient stimulus (Lepage, Saint-Amour, & Théoret, 2008), other studies fail to report this early modulation, suggesting that muscle-specific modulation can be induced only by late components of the mirror response (Cavallo, Heyes, Becchio, Bird, & Catmur, 2014). These findings have raised the intriguing hypothesis of a separation between early and late components of the mirror response (e.g., Candidi, Sacheli, Mega, & Aglioti, 2014; for a review, see Naish, Houston-Price, Bremner, & Holmes, 2014): an initial muscle-unspecific modulation would be followed by a later phase of modulation, which would be muscle-specific (Romani, Cesari, Urgesi, Facchini, & Aglioti, 2005) and then closely related to a motor resonance mechanism (Borgomaneri et al., 2014). Our findings, in agreement with the Fecteau et al. (2008) study, corroborate this two-stage hypothesis showing an effect of time on CS excitability.

The literature supporting the empathy for pain hypothesis, that is, that the same neural mechanism underpinning the perception of physical pain can be involved in the observation of others' pain (e.g., Lamm, Decety, & Singer, 2011; Valeriani et al., 2008; Godinho, Magnin, Frot, Perchet, & Garcia-Larrea, 2006; Avenanti et al., 2005; Singer et al., 2004) also suggests that self-related variables, such as the proximity and the tangibility of the observed pain, can play a crucial role in determining the empathetic experience (e.g., de Vignemont & Singer, 2006; Jackson, Rainville, & Decety, 2006). Along this line of research, for instance, Mahayana et al. (2014) have found, during the observation of others' pain, a significant corticospinal inhibition (i.e., reduction in MEP amplitude) for stimuli presented in peripersonal space and not for stimuli presented in extrapersonal space. The authors interpreted this proximity-related response as a consequence of the misidentification of sensory information as being directly related to the observer. The neural basis of a shared peripesonal space representation, including both self and other's body, has been described in monkeys (Ishida, Nakajima, Inase, & Murata, 2009) and in humans (Brozzoli, Gentile, Bergouignan, & Ehrsson, 2013). In the monkey, the activity of parietal bimodal neurons with receptive fields anchored on the monkey's body has been shown to exhibit visual responses matched to corresponding body parts of the experimenter (Ishida et al., 2009). In the human, a specific cluster of neurons in the ventral premotor cortex are active when visual stimuli enter the perihand space, irrespective of whether the observed hand, always positioned in first-person perspective, is the participant's own hand or that of another person (Brozzoli et al., 2013). A similar visual response to stimuli delivered within self and others' perihand space is particularly relevant in our experimental context, because the premotor cortex is only one synapse away from the motor cortex and can likely contribute to modulate its activity during MEP recording.

In the context of the empathy for pain hypothesis, the perspective-related constraint has never been investigated, and the hand model has been always presented in a first-person perspective. However, to corroborate the empathy for others' pain hypothesis, a pain-specific effect should also be found when the stimuli are presented in a third-person perspective, the one in which we usually perceive and interact with the body parts of others (e.g., Ruby & Decety, 2001). The notion about the importance of the perspective through which a body part is observed comes from the results of the embodiment-related literature, investigating the alterations of the sense of body ownership both in experimental manipulations in healthy participants and in pathological conditions after brain damage. One of the more compelling demonstrations of the mechanisms subserving body ownership has been obtained in healthy participants by means of an experimental procedure known as the RHI (e.g., Botvinick & Cohen, 1998). Essentially, watching a rubber hand being stroked while one's own unseen hand is stroked synchronously can lead to a sense of ownership over the rubber hand (as self-reported at the body ownership questionnaire) and to a shift in the perceived position of the real hand (as measured by the proprioceptive drift). Previous studies have shown that the illusion effect disappears when the fake hand is rotated (i.e., it is perceived from a third-person perspective) or misaligned with respect to the participant's shoulder (Kalckert & Ehrsson, 2012; Petkova et al., 2011; Costantini & Haggard, 2007; Lloyd, 2007; Austen, Soto-Faraco, Enns, & Kingstone, 2004; Ehrsson et al., 2004; Farnè, Pavani, Meneghello, & Làdavas, 2000; Pavani, Spence, & Driver, 2000). In brain-damaged participants, a monothematic delusion of body ownership has been described where patients treat and care for the examiner's hand as if it was their own, showing a consistent embodiment of the alien hand in their own body schema (Garbarini et al., 2013, 2014, 2015; Pia, Garbarini, Fossataro, Fornia, & Berti, 2013). This delusion of ownership, although resembling the RHI, is spontaneous and not induced by any experimental procedure. Interestingly, as for the rubber hand embodiment, this phenomenon occurs only when the alien hand is perceived in a first-person perspective and it is aligned with the patients' contralesional shoulder, exactly where it is normally expected to be. If the alien hand is perceived from a third-person perspective or it is misaligned with respect to the patient's shoulder, the pathological embodiment does not occur and patients correctly identify their own hand. In this study, the results of the additional RHI experiment, showing an illusory effect in the synchronous condition only when the fake hand was perceived in first-person perspective, clearly confirm the importance of the perspective-related constraint in triggering multisensory mechanisms leading to the bodily self-representation.

According to a philosophical definition of the term "Embodiment," "E is embodied if and only if some properties of E are processed in the same way as the properties of one's body" (de Vignemont, 2010). In line with this definition, by recording the skin conductance response during noxious stimulations, previous studies on the RHI in healthy participants (Guterstam, Petkova, & Ehrsson, 2011; Armel & Ramachandran, 2003) and on the pathological embodiment after brain damage (Garbarini et al., 2014) showed that an alien hand can be so deeply embedded into one's own somatosensory experience as to elicit physiological reactions specific to the own hands. In this study, we demonstrated that a motor response, comparable to that found when the participants receive nociceptive stimuli on their own body (freezing effect; Urban et al., 2004; Farina, Tinazzi, Le Pera, & Valeriani, 2003), also occurs when the nociceptive stimuli were delivered to someone else's hand, whenever it is perceived in a first-person perspective, automatically leading to a sort of embodiment. It has been proposed that, because previous studies examining corticospinal excitability when experiencing pain used methods (e.g., saline injection, electrical stimulation) that prevent preparation of appropriate pain avoidance reactions (Urban et al., 2004; Farina et al., 2001, 2003; Le Pera et al., 2001), an anesthetic motor inhibition is the most adaptive response (De Coster, Andres, & Brass, 2014). Accordingly, a situation in which participants passively observe pain delivered to a hand model may preclude the possibility to prepare an avoidance reaction to that pain and, therefore, can lead to a modulation of the corticospinal excitability in terms of inhibition rather than facilitation. Conversely, by manipulating the sense of agency over the observed hand model (always presented in first-person perspective) and by positioning the participants in a body posture allowing pain avoidance, a facilitation of the corticospinal system has been observed (De Coster et al., 2014).

In this study, we replicated the setup and stimuli proposed in previous studies (Avenanti et al., 2005, 2006, 2010; Avenanti, Minio-Paluello, Bufalari, et al., 2009) to compare first-person and third-person perspective and to disentangle an empathy and a body ownership interpretation. We acknowledge that the present setup of MEP recording was not optimally designed to elicit a full embodiment effect, as that observed during the RHI (Kalckert & Ehrsson, 2012; Petkova et al., 2011; Makin et al., 2008; Costantini & Haggard, 2007; Tsakiris & Haggard, 2005; Ehrsson et al., 2004; Botvinick & Cohen, 1998) or during the virtual hand illusion (Slater, Perez-Marcos, Ehrsson, & Sanchez-Vives, 2008). Indeed, for rubber/virtual hand illusion to work, the hand must be placed in an anatomically plausible position, at a maximum distance of 30 cm from the real hand (Costantini & Haggard, 2007). In future experiments, this could be achieved by placing the screen on the table and having the participant put his or her hand under the screen to create a "see-through" effect. A similar setup can also allow to carry out future experiments in which the observer's hand posture and the hand model visual perspective can be systematically manipulated to more deeply investigate the role of the postural congruency during MEP recording. The lack of a full embodiment effect can also be seen in the mean rating at the body ownership item, which, together with the pain first-person condition, did not reach values higher then zero (mean ± *SD* = −0.43 ± 2.06), contrary to what is usually reported when a full embodiment occurs. This means that participants seemed to be uncertain whether they experienced illusory ownership or not. On the contrary, the mean rating at the self-recognition item reaches rather high scores in the pain first-person condition (mean ± *SD* = 0.93 ± 1.56), suggesting that, in this condition, participants tended to consider the prick delivered to the hand model as if it was delivered to the hand they recognized as their own. However, both items showed similar pain and perspective effects in the ANOVA analysis and significantly greater ratings in the pain first-person condition with respect to all the other conditions. These behavioral results mirror the physiological results, showing that the MEP amplitude was significantly lower in the pain first-person condition with respect to all other conditions. Crucially, in the pain first-person condition, a significant correlation between physiological and behavioral data was found only when considering the body ownership item: The stronger the freezing effect, implicitly measured as a drop in the MEP amplitude recorded from the FDI muscle, the stronger the embodiment sensation, explicitly reported at the body ownership questionnaire. Furthermore, the significant correlation between the freezing effect in the pain first-person condition and the extent to which participants experienced the RHI in the synchronous first-person condition also suggests that a mechanism related to the concept of bodily ownership can play an important role in explaining the present data. This indicates a mutual interaction between our conscious beliefs about the body and the physiological mechanisms within the body.

It is worth noting that the perspective-dependent effect we describe only pertains to the pain condition at the late time of stimulation. A previous study investigating the perspective effect on motor imagery showed a greater facilitation of MEP recorded from FDI in third-person imagery, where the action was clearly attributable to another person, with respect to first-person imagery (Fourkas, Avenanti, Urgesi, & Aglioti, 2006). Together with our results, these findings showed lower values when MEPs were recorded in first-person compared with third-person perspective. Thus, it was crucial to investigate the presence of a nonspecific perspective effect. However, we did not find a significant perspective effect either at the early time of stimulation or in the touch condition. Furthermore, no difference was found between the baseline values recorded when the hand model was presented in first-person and third-person perspectives, suggesting absence of a nonspecific perspective effect.

The key finding of this study is that a pain-specific inhibition of MEP amplitude (i.e., a significantly greater MEP reduction in pain compared with touch conditions) only occurs in a first-person perspective. On the contrary, no difference between pain and touch conditions was found when stimuli were presented in a third-person perspective. Crucially, the corticospinal excitability was directly related both to the subjective embodiment disposition, as measured by the RHI, and to the extent to which the participants reported, while observing the hand model being penetrated, to feel "as if" the penetrated hand was part of their own body. On the contrary, unlike previous studies (Avenanti et al., 2005), in our sample no significant correlation between the index of MEP amplitude change and the empathetic traits, as reported at the IRI questionnaire, was found. Taken together, these findings suggest that the motor response of the onlooker can be better interpreted referring to the concept of body ownership than to the empathy for others' pain hypothesis. In particular, these data are suggestive of an "affective" conception of body ownership (de Vignemont, 2014), indicating that the body I feel as my own is the body I care more about, the one to which I react when under threat.

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Reprint requests should be sent to Francesca Garbarini, Department of Psychology, University of Turin, Via Po 14, 10123 Turin, Italy, or via e-mail: fra.garbarini@gmail.com, francesca.grabarini@unito.it.

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